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## Immunotherapy of gastric cancer with levamisole

Hiroaki Miwa\*

Kunzo Orita†

\*Okayama University,

†Okayama University,

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# Immunotherapy of gastric cancer with levamisole\*

Hiroaki Miwa and Kunzo Orita

## Abstract

Ninety-nine gastric cancer patients initially received levamisole at a daily dose of 150 mg for three consecutive days before operation. This therapy was repeated fortnightly (3-day administration followed by 11-day withdrawal period) for more than one month as long as possible and the survival rate up to 18 months was compared with that of control patients. The 18 month survival rate of advanced Stage IV patients was significantly higher in patients receiving levamisole than that of control patients. The effects of levamisole in cases of advanced cancer have been discussed in relation to the literature available.

**KEYWORDS:** levamisole, gastric cancer, immunotherapy

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## IMMUNOTHERAPY OF GASTRIC CANCER WITH LEVAMISOLE

Hiroaki MIWA and Kunzo ORITA

*Department of Surgery, Okayama University Medical School,  
Okayama 700, Japan*

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**Abstract.** Ninety-nine gastric cancer patients initially received levamisole at a daily dose of 150 mg for three consecutive days before operation. This therapy was repeated fortnightly (3-day administration followed by 11-day withdrawal period) for more than one month as long as possible and the survival rate up to 18 months was compared with that of control patients. The 18 month survival rate of advanced Stage IV patients was significantly higher in patients receiving levamisole than that of control patients. The effects of levamisole in cases of advanced cancer have been discussed in relation to the literature available.

**Key words:** levamisole, gastric cancer, immunotherapy

Immunotherapy has only recently begun to be used as a form of cancer therapy, nevertheless with the rapid and remarkable progress in immunotherapy with bacillus Calmette-Guérin (BCG), cancer immunotherapy with immunostimulators extracted from organism holds much promise for the future. In our previous studies, we treated cancer patients with levamisole, (commonly used as anthelmintic in Europe and the United States) which was shown first by Renoux and Renoux (1) to have a stimulating effect on immunity and found in a small number of cases that therapy with levamisole stimulated the depressed immunity of cancer patients relatively rapidly (2) and also increased the survival rate (3).

This paper is concerned with the investigation of the antitumor effects of levamisole in gastric cancer patients at relatively clearly defined stages of the disease. This is the first report in which therapy with levamisole has definitely been shown to increase survival rate of far advanced (Stage IV) gastric cancer patients.

### MATERIALS AND METHODS

Ninety-nine patients with gastric cancer admitted to our Department of Surgery and subjected to operation were studied. The patients were classified into Stages I to IV according to the advance of gastric cancer (4). Of these 99, 19 were

in Stage I, 13 in Stage II, 29 in Stage III and 38 in Stage IV cancer. The patients were also classified by the resectability of the tumor: curative resection in 57, noncurative resection in 35 and no resection in 7. Control subjects consisted of 220 gastric cancer patients (36 in Stage I, 29 in Stage II, 51 in Stage III, 104 in Stage IV, Curative resection in 122, noncurative resection in 62, no resection in 31) admitted to our Department and subjected to operation between 1971 and 1976. Gastric cancer Stage IV patients of levamisole-treated and control groups consisted respectively of 7 and 15 in curative resection, 24 and 58 in noncurative resection and 7 and 31 without resection. None of these control patients were treated with levamisole or any other known immunostimulator. The age distribution, method of operation and form of cancer therapy in the control group were similar to those in the levamisole-treated group.

The standard course of treatment with levamisole consisted of oral administration of 150 mg daily for 3 consecutive days starting 3 days before operation and repeated fortnightly (3-day administration followed by 11-day withdrawal period) for more than 1 month and as long as possible.

Statistical analysis of the data on postoperative survival was done by applying the " $\chi^2$ " test between the levamisole and control groups.

## RESULTS

*Six-month survival rate.* In both the levamisole group and the control group, a decrease in the 6-month survival rate was observed with advancing stages of cancer, but the survival rate in the levamisole group did not decrease to a larger extent than that in the control group. Application of the " $\chi^2$ " test, however, showed no significant difference in the survival rate between the 2 groups at any stage (Table 1, Fig. 1).

*Twelve-month survival rate.* The 12-month survival rates for the 2 groups decreased with advancing stages of cancer similar to the 6-month survival rates. The 12-month survival in Stage I, II and III patients was not significantly higher in the levamisole group than in the control group, however, in Stage IV, the survival rate in the levamisole group was 68.8% (11/16) compared to 45.2% (47/104) in the control group and the difference was highly significant ( $\chi^2 = 3.08$ ,  $0.05 < p < 0.1$ ) (Table 1, Fig. 1).

*Eighteen-month survival rate.* Because of an extremely small number of patients in Stage I and II, an analysis of the results will await further studies. However, from the results there was no significant difference in the 18-month survival rate in Stage III between the levamisole and control groups, the same may be estimated regarding either Stage I or II patients. As for Stage IV, the survival rate in the levamisole group was 53.3% (8/15) as compared to a 27.2% (28/103) in the control group. The difference was statistically highly significant ( $\chi^2 = 4.22$ ,  $0.02 < p < 0.05$ ), indicating that the trend observed in the 12-month survival rate was amplified. In view of the above, levamisole appears

TABLE 1. SURVIVAL RATES FOR STAGE I-IV GASTRIC CANCER PATIENTS

Stage of gastric cancer	6-month survival					12-month survival					18-month survival				
	Control		Levamisole		$\chi^2$ test	Control		Levamisole		$\chi^2$ test	Control		Levamisole		$\chi^2$ test
	No.	%	No.	%		No.	%	No.	%		No.	%			
I	36/36	100.0	12/12	100.0	$\chi^2=0$ $p>0.5$	35/35	100.0	6/6	100.0	$\chi^2=0$ $p>0.5$	29/29	100.0	1/1	100.0	NS
II	28/29	96.6	9/9	100.0	$\chi^2=0.32$ $p>0.5$	28/29	96.6	6/6	100.0	$\chi^2=0.21$ $p>0.5$	23/24	95.8	4/4	100.0	NS
III	48/51	94.1	24/25	96.0	$\chi^2=0.12$ $p>0.5$	42/51	82.4	18/20	90.0	$\chi^2=0.64$ $0.2<p<0.5$	36/50	72.0	12/14	85.7	$\chi^2=1.10$ $0.2<p<0.5$
IV	75/104	72.1	23/26	89.5	$\chi^2=1.79$ $0.1<p<0.2$	47/104	45.2	11/16	68.8	$\chi^2=3.08$ $0.05<p<0.1$	28/103	27.2	8/15	53.3	$\chi^2=4.22$ $0.02<p<0.05$

to be more effective in cases of advanced cancer (Table 1, Fig. 1).

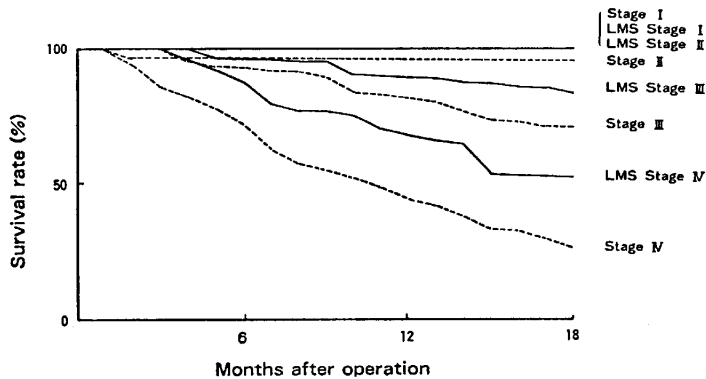


Fig. 1. Survival curves up to 18 months after operation for gastric cancer. —, levamisole group; ----, control group; LMS, levamisole.

#### DISCUSSION

Since the antitumor effects of levamisole were reported first by Renoux *et al.* in C57BL mice with Lewis lung (3LL) tumor (5), much work has been done on this subject. Symoens (6), summarizing these reports, concluded that levamisole has no definite effect on the proliferation or metastasis of primary tumor of transplanted animal cancers but prevents relapse if it is administered after the tumor cells have been reduced by other measures.

With regard to the effects of levamisole on human cancer, there have been only a few reports of effective cases in lung cancer and breast cancer and there has yet been no report dealing with its effects on gastric cancer. The Study Group for Brochogenic Carcinoma under the leadership of Amery (7) treated patients with bronchogenic carcinoma with levamisole in the same manner as ours and observed inhibited relapse and prolonged survival. They also found that the effects of levamisole were more marked in patients whose excised tumors had been larger in the longest diameter. Rojas *et al.* (8) continued a course of therapy with levamisole consisting of 3 consecutive daily doses of 150 mg followed by an 11-day withdrawal in a group of patients with inoperable Stage III breast cancer following radiotherapy. At 24 weeks post-radiotherapy, 50% of the patients receiving continued courses of levamisole had no relapse of disease while only 9% of control patients were free from disease. The results were in good agreement with the prolonging effect of levamisole on survival in their series of patients. Debois (9) also studied the effects of levamisole in breast cancer patients who received either radiotherapy alone or radiotherapy combined with levamisole at a daily dose of 150 mg, (3-day treatment plus 11-day withdrawal) and compared

the 25-month survival rates of the 2 groups. The observed result that levamisole was highly effective in cases of advanced Stage IV cancer resembles closely our findings in gastric cancer patients. Also there have been a report of cases with satisfactory results by Renoux and Renoux (10) and that of failure by Lichtenfeld *et al.* (11).

In its human cancer application, some measures for reducing tumor cells are necessary to obtain satisfactory results with levamisole therapy.

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